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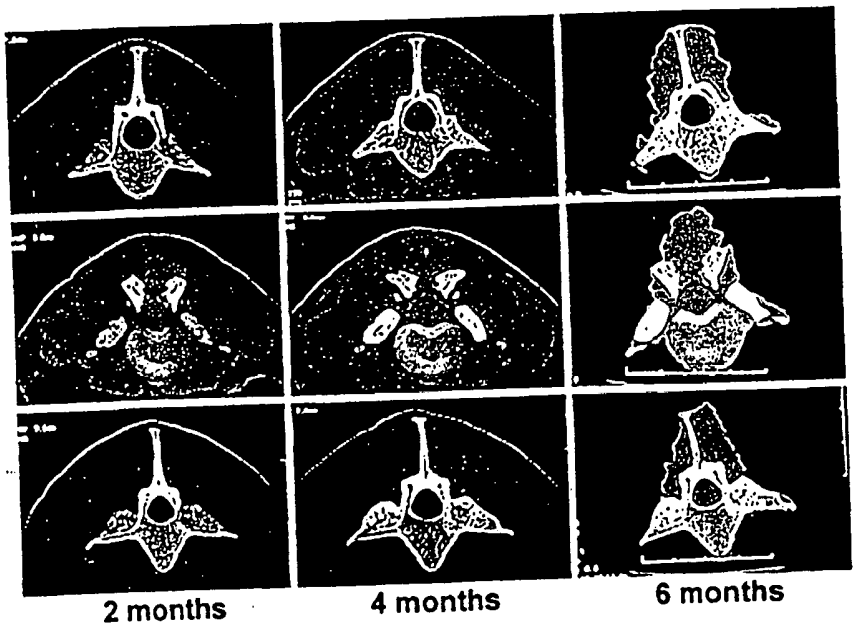
(54) Title: HIGHLY-MINERALIZED OSTEOGENIC SPONGE COMPOSITIONS, AND USES THEREOF



(57) Abstract

Osteogenic sponge compositions having enhanced osteoinductive properties for use in bone repair are described. The compositions include a quickly resorbable porous carrier, a more slowly resorbed mineral scaffold and an osteogenic factor, preferably a bone morphogenetic protein. The compositions enable increased osteoinductive activity while retaining a reliable scaffold for the formation of new bone at an implant site. Methods for therapeutic use of the compositions are also described.

HIGHLY-MINERALIZED OSTEOGENIC SPONGE COMPOSITIONS, AND USES THEREOF

REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Patent Application Serial No. 60/118,615 filed February 4, 1999, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates generally to osteogenic compositions. Specifically, the present invention relates to an osteogenic sponge composition effective for the induction of new bone growth in animals.

BACKGROUND OF THE INVENTION

Bone grafting has been commonly used to augment healing in the treatment of a broad range of musculoskeletal disorders. This procedure has several disadvantages. If the bone material is obtained from donors of the same species, such as an allograft, an increased risk of disease transmission and immune reaction exists. Bone material surgically removed from the patient, known as an autograft, is also undesirable because a sufficient amount of autogenous bone may not be available and the additional surgery necessary to obtain the autograft increases the risk of infection.

Due to the need for safer bone graft materials, efforts have been directed to finding bone graft substitutes. Candidate compositions include collagen and a bioceramic, such as hydroxyapatite, as these

SUMMARY OF THE INVENTION

The invention provides in one preferred embodiment an osteogenic sponge composition useful for the induction of new bone growth in a mammal. This composition includes a resorbable sponge matrix material and an osteogenic factor, preferably one that preferably stimulates osteoblasts and osteoclasts, said osteogenic factor incorporated in the sponge matrix material. The resorbable sponge matrix material is desirably a three-dimensionally stable yet flexible material, facilitating its use as an implant. The osteogenic factor is usually incorporated in an amount that causes an increased rate of resorption of said sponge matrix material in a mammal. The composition also includes a particulate mineral having an average particle diameter of at least about 0.5 mm embedded in the resorbable sponge matrix material, wherein the particulate mineral present in a weight ratio of at least 4:1 relative to the resorbable sponge matrix material so as to provide a scaffold for bone ingrowth in the presence of the osteogenic factor. More preferred compositions are even more highly mineralized, for example wherein the particulate mineral is present in a weight ratio of at least about 10:1 relative to the resorbable sponge matrix material. The particulate mineral is desirably formed of a synthetic calcium phosphate ceramic or of bone, especially cortical bone. The osteogenic factor is most preferably BMP-2 or LMP, or comprises a nucleotide sequence encoding BMP-2 or LMP.

Another embodiment of the present invention provides a method for inducing bone growth in a primate. The method includes a first step of providing an osteogenic sponge composition having a

collagen and 97% to 99% by weight of the particulate biocompatible mineral. In another inventive feature, an osteogenic factor can be incorporated in such an implant.

A further embodiment of the invention provides an interbody spinal fusion device that includes a load bearing member sized for insertion between adjacent vertebrae and any one of the aforementioned compositions retained by the load bearing member. Such fusion devices can be used in inventive interbody spinal fusion methods mammals, wherein the devices are appropriately implanted to facilitate spinal fusion.

A particular feature of the present invention relates to the discovery that the inclusion of an osteogenic factor, especially an osteoblast- and osteoclast-stimulating osteogenic factor, in a resorbable sponge composition causes a substantially accelerated resorption of the sponge. This rapid resorption can diminish or eliminate the capacity of the sponge composition to effectively stimulate and support new bone formation in a void filled with the sponge composition. This is particularly the case in primates, including humans, in which the rate of new bone formation is relatively slow. Objects of the present invention are to provide osteogenic sponge compositions effective for the induction of bone growth in mammals, particularly primates, including humans, and related methods and devices. These and other objects and advantages of the present invention will become apparent upon reading the descriptions herein.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

For the purposes of promoting an understanding of the principles of the invention, reference will now be made to preferred embodiments and specific language will be used to describe the same. It will nevertheless be understood that no limitation of the scope of the invention is thereby intended, such alterations and further modifications of the invention, and such further applications of the principles of the invention as illustrated herein, being contemplated as would normally occur to one skilled in the art to which the invention relates.

As described above, the invention relates in certain aspects to osteogenic sponge compositions effective for the induction of new bone growth in mammals and methods for inducing bone growth in mammals. The present invention features osteogenic sponge compositions effective for use in primates, wherein the compositions exhibit high osteoinductive potential and provide a lasting mineral scaffold to support bone ingrowth. Such preferred compositions include a porous, resorbable sponge carrier, such as collagen in sponge form, and an osteogenic factor that stimulates the action of both osteoblasts (which biologically facilitate the formation of bone) and osteoclasts (which biologically facilitate the resorption of bone). In accordance with the present invention, it has been found that the incorporation of an effective inductive amount of an osteogenic factor, such as a bone morphogenetic protein (BMP), stimulates osteoclasts to such a level that a porous resorbable carrier is quickly resorbed and, in the absence of a high mineral component in the composition, causes the performance of the composition to suffer in some cases to the extent that the observation of substantial bone

The collagen carrier can further be atelopeptide collagen and/or telopeptide collagen. Moreover, both non-fibrillar and fibrillar collagen may be used. Non-fibrillar collagen is collagen that has been solubilized and has not been reconstituted into its native fibrillar form.

The sponge carrier may also be formed of other natural or synthetic polymeric materials, in addition to or as an alternative to collagen. For example, the sponge carrier may be formed of gelatin (e.g. foamed gelatin), in addition collagen or as an alternative to collagen. Other natural and synthetic polymers are also known for the formation of biocompatible sponge materials, and can be used herein.

As indicated above, preferred compositions of the invention also include an osteoinductive factor, such as an osteoinductive protein or a nucleotide sequence encoding an osteoinductive protein operably associated with a promoter (e.g. provided in a vector such as a viral vector) which drives expression of the gene in the animal recipient to produce an effective amount of the protein. The osteogenic factor utilized in the present invention can be one that stimulates production or activity of osteoblasts and osteoclasts. The factor is preferably a bone morphogenetic protein (BMP) or a LIM mineralization protein (LMP), or comprises a nucleotide sequence encoding a BMP or LMP. Recombinant human BMPs are preferred, and may be commercially obtained or prepared as described and known in the art, e.g. in U.S. Patent Nos. 5,187,076 to Wozney et al.; 5,366,875 to Wozney et al.; 4,877,864 to Wang et al.; 5,108,932 to Wang et al.; 5,116,738 to Wang et al.; 5,013,649 to Wang et al.; 5,106,748 to Wozney et al; and PCT Patent Nos.

calcium phosphate with have a tricalcium phosphate:hydroxyapatite weight ratio of about 50:50 to about 95:5, more preferably about 70:30 to about 95:5, even more preferably about 80:20 to about 90:10, and most preferably about 85:15.

In general, the amount of mineral in the osteogenic sponge composition must be sufficient to provide a scaffold that will remain in the patient for a period of time sufficient for the formation of osteoid in the void for which bone growth is desired. Typically, this period of time will be about 6 to about 8 weeks. The minimum level of mineral that must be present in the composition is also dependent on the activity of the BMP in the composition; the higher the activity of the BMP, the greater the content of the mineral matrix required to counter the osteoclastic potentiation of the BMP. The rate of resorption of the resorbable carrier also increases as the BMP concentration increases.

In preferred aspects of the invention, the particulate mineral:resorbable sponge matrix weight ratio will be at least about 4:1, more preferably at least about 10:1. In particularly preferred sponge implants, the particulate mineral will constitute at least 95% by weight of the sponge implant. For example, highly effective sponge carrier devices are provided wherein they comprise about 97% to about 99% by weight particulate mineral and about 1% to about 3% of the collagen or other sponge-forming matrix material. Moreover, it is preferred that the mineral component have an average particle size of at least about 0.5 mm, more preferably about 0.5 mm to about 5 mm, and most preferably about 1 mm to about 3 mm.

growth in mammals are provided. The methods include providing the above-described osteogenic sponge composition and implanting the composition at a site at which bone growth is desired, e.g., to treat a disease, defect or location of trauma, and/or to promote artificial arthrodesis. The hydrated sponge composition may be rolled up prior to packing the sponge into the implantation site.

Once in place, the osteogenic sponge composition will effectively induce and support ingrowth of bone into the desired area even in a primate such as a human that exhibits a relatively slow rate of bone formation compared to smaller mammals, such as rodents or rabbits. Although the collagen carrier is resorbed relatively quickly, the substantial mineral component remains as a scaffolding to support new bone growth in and through the desired area.

The above osteogenic sponge compositions of the present invention are especially advantageous when used in bones or bone portions that exhibit only low to moderate vascularization. Such low to moderate vascularized regions exhibit low rates of bone formation so rapid resorption of a carrier poses a problem. Examples of low to moderate vascularized sites include, for example, transverse processes or other posterior elements of the spine.

An especially preferred use of the sponge compositions of the present invention is as an implant to promote arthrodesis between vertebrae in spinal fusions in humans or other primates, including interbody, posterior and/or posterolateral fusion techniques. Although the rate of bone formation in the primate spine is relatively slow overall and thus will benefit generally from the present invention, the elements to be fused in posterior and

EXAMPLE 2
PREPARATION OF COLLAGEN SPONGE/ SYNTHETIC CERAMIC COMPOSITE

12 grams of biphasic calcium phosphate particles, 1 mm in diameter, were added to 12 grams of collagen slurry (0.192 grams of collagen). This composite slurry was poured into a 7.5 cm x 10.0 cm mold, freeze dried, double sterile packaged, and sterilized by ETO gas sterilization.

EXAMPLE 3
PREPARATION OF COLLAGEN SPONGE/ BONE PARTICLE COMPOSITE

12 grams of deproteinized cortical bone chips, 1-3 mm in size, were added to 24 grams of collagen slurry (0.192 grams of collagen). This composite slurry was poured into a 7.5 cm x 10.0 cm mold, freeze dried, double sterile packaged, and sterilized by ETO gas sterilization.

EXAMPLE 4
PREPARATION OF COLLAGEN SPONGE/ SYNTHETIC CERAMIC COMPOSITE

12 grams of biphasic calcium phosphate particles, 1 mm in diameter, were added to 24 grams of collagen slurry (0.192 grams of collagen). This composite slurry was poured into a 7.5 cm x 10.0 cm mold, freeze dried, double sterile packaged, and sterilized by ETO gas sterilization.

were placed bilaterally, with two sponges (one on top of the other) on each side of the spine, resulting in a total dose of 9 mg rhBMP-2 per implant site. The animals were allowed to recover and move around ad libitum without restrictions during the study period.

The spines were manually assessed for fusion upon sacrifice (2, 4 and 6 months) and determined to be fused based upon the absence of motion during attempted bending, and presence of histological bridging bone.

The fusions were also evaluated by CT scan at 2, 4 and 6 months after implantation. FIGS. 1 and 2 show the CT scans for each subject studied. FIGS. 1 and 2 demonstrate the sequence of events that occur within the composite sponge carrier loaded with rhBMP-2. On the far left of the figures are three CT sections equally spaced throughout the fusion mass at 2 months post-operative, showing that resorption of the composite sponge is just about complete due to the lack of radiopacity of the ceramic granules. The three middle CT sections show these same three CT sections at four months with increased bone deposition where the carrier once resided. The composite sponge has maintained the space within the soft tissue site for a sufficient enough period of time for the desired volume of new bone deposition to occur. Finally, the far right three CT scans show even further bone deposition, remodeling and maturation with the formation of outer cortices around the periphery of the fusion masses by six months.

6. The osteogenic sponge composition of claim 1, wherein said particulate mineral is selected from the group consisting of bone particles and biocompatible synthetic calcium phosphate ceramics.

7. The osteogenic sponge composition of claim 6, wherein said particulate mineral comprises biphasic calcium phosphate.

8. The osteogenic sponge composition of claim 7, wherein said biphasic calcium phosphate has a porosity of at least about 50%.

9. The osteogenic sponge composition of claim 8, wherein said particulate mineral includes bone particles.

10. The osteogenic sponge composition of claim 9, wherein said bone particles are cortical bone particles.

11. The osteogenic sponge composition of claim 1, which is comprised at least about 95% by weight of said particulate mineral.

12. The osteogenic sponge composition of claim 1, wherein said particulate mineral has an average particle size in the range of about 0.5 mm to about 5.0 mm.

13. The osteogenic sponge composition of claim 1, wherein said porous particulate mineral has an average particle size in the range of about 1 to about 2 mm.

14. The osteogenic sponge composition of claim 1, wherein said osteogenic factor is a bone morphogenetic protein.

20. A method for inducing bone growth in a primate, comprising:

(a) providing an osteogenic sponge composition comprising:

a resorbable sponge matrix material;

an osteogenic factor that stimulates osteoblasts and osteoclasts, said osteogenic factor incorporated in said sponge matrix material in an amount that causes an increased rate of resorption of said sponge matrix material in the primate; and

particulate mineral having an average particle diameter of at least about 0.5 mm embedded in said resorbable sponge matrix material, said particulate mineral present in a weight ratio of at least 4:1 relative to said resorbable sponge matrix material, so as to provide a scaffold for bone ingrowth in the presence of said ostegenic factor; and

(b) implanting said osteogenic sponge composition in an area in which bone growth is desired in the primate, said osteogenic sponge composition providing a scaffold for a duration sufficient for osteoid ingrowth through an area in which said osteogenic sponge composition is implanted.

21. The method of claim 20, wherein said particulate mineral is present in a weight ratio of at least 10:1 relative to said resorbable sponge matrix material.

22. The method of claim 21, wherein said osteogenic factor comprises a bone morphogenetic protein, a LIM mineralization protein, or a nucleotide sequence encoding a bone morphogenetic protein or LIM mineralization protein.

32. The method of claim 20, wherein said porous particulate mineral has an average particle size of about 1 to about 2 mm.

33. The method of claim 20, wherein said osteogenic factor is a bone morphogenetic protein.

34. The method of claim 33, wherein said bone morphogenetic protein is a recombinant human protein.

35. The method of claim 33, wherein said bone morphogenetic protein is BMP-2 or BMP-7.

36. The method of claim 20, wherein the primate is a human.

37. The method of claim 20, wherein the area is in the spine of said primate.

38. The method of claim 37, wherein the bone growth is induced to attain a spinal fusion.

39. The method of claim 38, wherein the spinal fusion is an interbody spinal fusion.

40. The method of claim 38, wherein the spinal fusion is a posterolateral spinal fusion.

41. The method of claim 38, wherein the spinal fusion includes a fusion between transverse processes of adjacent vertebrae.

48. An osteogenic implant, comprising:

a resorbable matrix carrier comprised 1% to 3% by weight of collagen in sponge form and 97% to 99% by weight of a particulate biocompatible mineral embedded within said collagen; and

an osteogenic factor.

49. An interbody spinal fusion device, comprising:

a load bearing member sized for insertion between adjacent vertebrae; and

a composition according to any of claims 1-19 and 42-48 retained by said load bearing member.

50. A method for interbody spinal fusion in a mammal, comprising implanting between adjacent vertebrae in the mammal an interbody spinal fusion device according to claim 49.

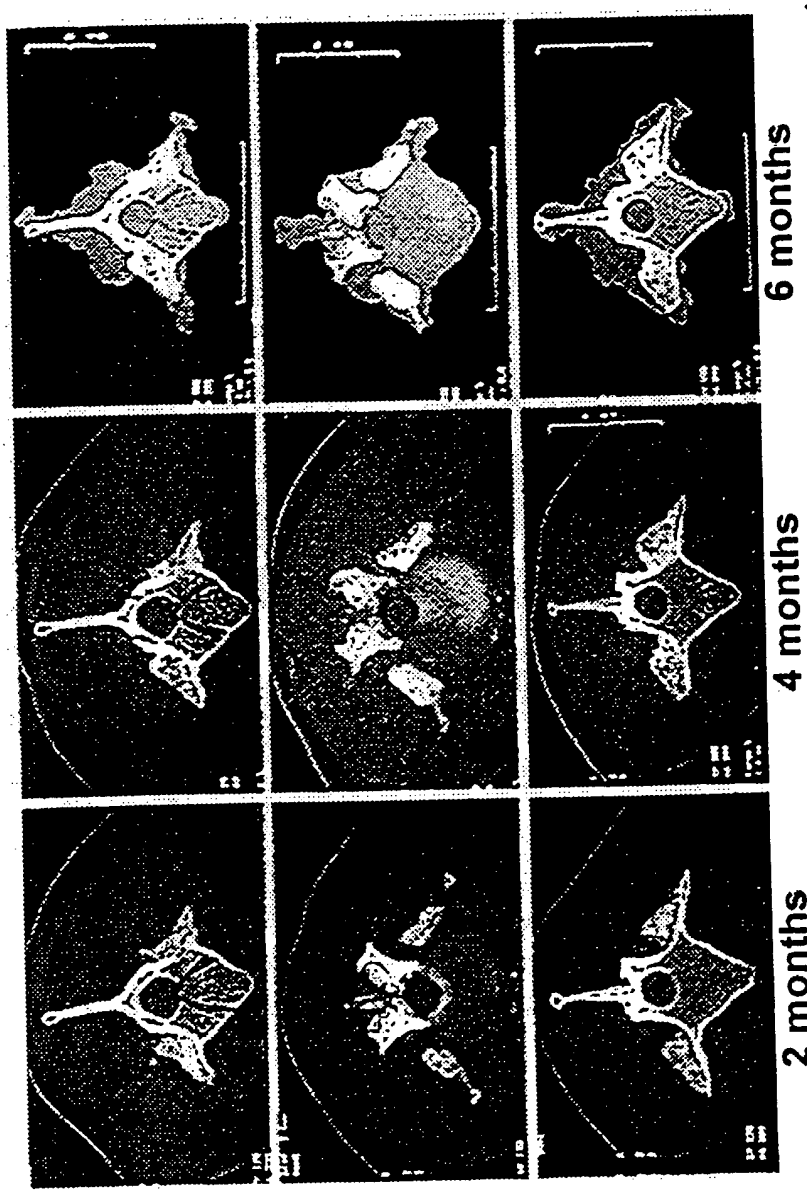


Fig. 2

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/03043

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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Information on patent family members

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